Complete Summary

GUIDELINE TITLE

Guidance on the use of paclitaxel in the treatment of ovarian cancer.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of paclitaxel in the treatment of ovarian cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 Jan. 19 p. (Technology appraisal guidance; no. 55).

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Guidance on the use of taxanes for ovarian cancer. London (UK): National Institute of Clinical Excellence (NICE); 2000 May. (Technology appraisal 3).

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Ovarian cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Advanced Practice Nurses
Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To review the use of paclitaxel (Taxol®) as first-line treatment of ovarian cancer

TARGET POPULATION

Women with ovarian cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Paclitaxel in combination with a platinum-based compound

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Overall response (complete response + partial response)
    - Progression free survival
    - Overall survival
    - Symptom relief
    - Quality of life
    - Adverse effects
- Cost

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York (See the "Companion Documents" field.)

Search Strategy

The following databases were searched for relevant literature:

- MEDLINE
- EMBASE
- CancerLit
- Cochrane Controlled Trials Register
- National Research Register

More detailed information about the search strategy is presented in Appendix 2 of the Assessment Report (see the "Availability of Companion Documents" field). Results of the database searches were deduplicated against results of the database searches for the original review, and only references which were not found in the original searches were assessed for inclusion.

Bibliographies of all retrieved articles were searched for additional references. Manufacturer and sponsor submissions made to the National Institute for Clinical Excellence (NICE) were also reviewed to identify any additional trials. The internet was searched for information on ongoing trials (see Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]).

Inclusion and Exclusion Criteria

Titles (and where possible abstracts) of trials identified from all searches and sources (see Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]) were assessed independently by two reviewers for relevance. If either reviewer considered the paper to be potentially relevant, a full paper copy of the manuscript was obtained. Each full paper copy was reassessed for inclusion using the same criteria as for the original review, which were as follows:

Interventions

a. Paclitaxel (Taxol ® Bristol-Myers Squibb) used either alone or in combination with other drugs as part of a chemotherapy regimen
b. Other standard chemotherapy regimens. For ovarian cancer these include non-platinum drugs such as cyclophosphamide, doxorubicin (Adriamycin), and platinum (cisplatin and carboplatin) either alone or in combination.

The use of taxanes as part of high dose regimens with autologous stem cell support was not considered. Trials comparing only different paclitaxel regimens (either in terms of dose, period of administration, or combination) were not included.

Participants

(See Appendix 1 of the Assessment Report [see the "Availability of Companion Documents" field] for definition of stages)

Women with ovarian cancer

a. Early (FIGO stage I)
b. Advanced (FIGO stages II to IV)

Outcomes

a. Overall response (complete response + partial response)
b. Progression free survival
c. Overall survival
d. Symptom relief
e. Quality of life
f. Adverse effects
g. Cost

Design

a. Randomised, controlled trials comparing paclitaxel to a standard chemotherapy regimen
b. Full economic evaluations

Trials comparing only different doses or period of infusion of taxanes were not included.

Trials that did not meet all of the criteria were excluded and their bibliographic details listed in Appendix 8 of the Assessment Report (see the "Availability of Companion Documents" field), along with the reason for exclusion. Information relating to inclusion of trials highlighted by the industry submissions is presented in Appendix 9 of the Assessment Report (see the "Availability of Companion Documents" field). Any disagreements were discussed in order to obtain a consensus and if no agreement was reached, a third reviewer was consulted.

NUMBER OF SOURCE DOCUMENTS

The original searches identified 2250 articles related to the taxanes. After independent assessment against the inclusion criteria by two reviewers, it was agreed that 213 references were to be obtained. The update searches identified a further 1290 articles related to the taxanes. After independent assessment against the inclusion criteria by two reviewers, 80 additional references were obtained. On examination of the obtained papers and reports, seven randomised controlled trials (RCTs) (including 4108 participants) and 15 economic evaluations were selected for review (includes both original and update searches).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York (See the "Companion Documents" field.)

Data Extraction Strategy

Data extraction was conducted by one reviewer using predefined data extraction forms in a Microsoft Access database and checked by a second reviewer. Any disagreement was resolved by consensus and, if this was not reached, a third reviewer was consulted.

The type of data that was extracted and summarised included specific details about the interventions, the population investigated, and the outcome measures used. Trials that had been reported in multiple publications were collated and reported only once.

Where sufficient data were presented, an estimation of the treatment effect along with the 95% confidence interval (CI) was calculated for each individual trial. Where possible this was done on an intention to treat basis. For dichotomous outcome measures the relative risk (RR) or hazard ratio (HR) was calculated and for continuous outcomes the median or mean difference (MD) was used. For survival data or other time-to-event data the hazard ratio was reported where presented in the included trial. If Kaplan Meier curves were presented, the p value of the log rank test was presented, where performed. Median survival times were also reported, where given in the trial.

In order to assess the economic data in terms of the clinical effectiveness of the intervention (i.e., the direction of the cost-effectiveness data and the magnitude of effectiveness data), each trial was given a summary grading (A-I) according to the level and direction of dominance (i.e. whether the intervention of interest should be preferred over the comparator). Extended dominance indicates that both the effectiveness data and the economic data support the use of either the intervention or the comparator and the decision on resource allocation is clear. When either the economic or the effectiveness data supports the intervention/comparator, the dominance is said to be partial or weak and a decision can still be made. However, if there is no dominance indicated then further incremental cost analysis may be required in order to estimate the incremental cost-effectiveness ratio. This is important in helping the decision-making process. Figure 1 in the Assessment Report (see the "Availability of Companion Documents" field) illustrates all of the possible permutations, and was used to assign each trial a summary grading.

Quality Assessment Strategy

The methodological quality of each included trial was assessed using predefined checklists. Two reviewers conducted this process independently. Any disagreements were resolved by consensus and a third reviewer was consulted if required. Quality criteria included method of randomisation, allocation concealment, baseline comparability of identified prognostic characteristics (which were identified as being treatment free interval, disease bulk, number of previous regimens, age, histology and performance status), presentation of eligibility criteria, reporting of co-interventions, loss to follow-up <20%, handling of withdrawals and use of intention to treat analysis. Blinding was also assessed, although it is acknowledged that blinding is often impossible in trials of cancer treatment.

Methods of Analysis/Synthesis

Results of data extraction and quality assessment are presented in structured tables and also as a narrative summary. Where new trials were found which impact on the results of the original review, the results of the original review are also presented.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Eleven cost-effectiveness analyses and three cost–utility analyses were available as evidence on the first-line use of paclitaxel. All were based on trials favouring paclitaxel (that is, GOG111 or OV10), and therefore found the paclitaxel/platinum combination to be more costly and more effective than control treatments. Three of the analyses could be directly applied to the United Kingdom.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is recommended that paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer.
- The choice of treatment for first-line chemotherapy for ovarian cancer should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options available. In choosing between treatment with a platinum-based compound alone or paclitaxel in combination with a platinum-based compound, this discussion should cover the side-effect profiles of the alternative therapies, the stage of the woman's disease, the extent of surgical treatment of the tumour, and disease-related performance status.
- When relapse occurs after an initial (or subsequent) course of first-line chemotherapy, additional courses of treatment with the chosen chemotherapy regimen (re-challenge therapy) should be considered if the initial (or previous) response has been adequate in extent and duration. Once the tumour fails to respond adequately to the chosen first-line regimen, different treatment options should be considered as part of second-line therapy (see below).
- Paclitaxel is not recommended as second-line (or subsequent) therapy in women with ovarian cancer who have received the drug as part of their first-line treatment. For women who have not received paclitaxel as part of first-line treatment, it should be considered as one option alongside other drugs licensed for second-line treatment of ovarian cancer.
- Only oncologists specialising in ovarian cancer should supervise the provision of chemotherapy in ovarian cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of paclitaxel in women with ovarian cancer, to increase response to treatment, survival and quality of life

POTENTIAL HARMS

Special Warnings and Special Precautions for Use

- Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.
- Patients must be pretreated with corticosteroids, antihistamines and H2 antagonists.
- Taxol should be given before cisplatin when used in combination.
- Hypersensitivity reactions: Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angiodema and generalised urticaria have occurred in < 1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine mediated. In the case of severe hypersensitivity reactions, paclitaxel should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.
- Haematological: Bone marrow suppression (primarily neutropenia) is the dose limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to a level $\geq$ 1.5 x 10^9/L and the platelets recover to a level $\geq$ 100 x 10^9/L.
- Cardiovascular: Severe cardiac conduction abnormalities have been reported rarely. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. Hypotension, hypertension and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.
- Nervous system: Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is unusual. In severe cases, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel.
- Patients with liver impairment: There is no evidence that the toxicity of paclitaxel is increased when given as a 3 hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment.
- Paclitaxel is not recommended for patients with severely impaired hepatic function.

- Other: Since paclitaxel contains dehydrated alcohol (396 mg/mL), consideration should be given to possible central nervous system and other effects.
- Special care should be taken to avoid intra-arterial administration of paclitaxel. In animal trials investigating local tolerance, severe tissue reactions occurred following intra-arterial administration.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Paclitaxel is contra-indicated in patients with severe hypersensitivity reactions to paclitaxel or any other component of the formulation, especially polyethoxylated castor oil.
- Paclitaxel is contra-indicated during pregnancy and lactation.
- Paclitaxel should not be used in patients with baseline neutrophils < 1.5 x 10^9/L.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation

- Clinicians with responsibility for treating women with ovarian cancer should review their current practice in line with the guidance (see the "Major Recommendations" field).
- Local guidelines, protocols, or care pathways on the care of women with ovarian cancer should incorporate the guidance (see the "Major Recommendations" field).
- To measure compliance locally with the guidance, the following criteria can be used. Further details on audit criteria are presented in Appendix D of the original guideline document.
    - First-line chemotherapy (usually following surgery) in the treatment of ovarian cancer includes the options of paclitaxel in combination with a platinum-based compound or platinum-based therapy alone.
    - The choice of treatment for first-line chemotherapy for an individual woman with ovarian cancer is based on discussion between the woman and the responsible clinician regarding the risks and benefits of the

options available. The following issues should be discussed: side-effect profiles of the alternative therapies, the stage of the woman's disease, the extent of surgical treatment of the tumour, and disease-related performance status.
    - Additional courses of treatment with the chosen chemotherapy regimen are offered to women following relapse after the initial (or subsequent) course of first-line treatment, if the extent and duration of the initial (or previous) response is adequate.
    - Paclitaxel is considered as second-line (or subsequent) treatment for women with ovarian cancer only if they have not received the drug previously as part of first-line treatment.
    - Only oncologists specialising in ovarian cancer supervise the provision of chemotherapy in ovarian cancer.
- Local clinical audits on the management of ovarian cancer also could include measurement of compliance with accepted clinical guidelines or protocols or with the measures for the treatment of ovarian cancer that are suggested in *Improving Outcomes in Gynaecological Cancers, Guidance on Commissioning Cancer Services*.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of paclitaxel in the treatment of ovarian cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 Jan. 19 p. (Technology appraisal guidance; no. 55).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 May (revised 2003 Jan)

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor R L Akehurst, Dean, School of Health Related Research, Sheffield University; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Professor Sir Colin Berry, Professor of Morbid Anatomy St Bartholomew's and Royal London School of Medicine; Dr Sheila Bird, MRC Biostatistics Unit, Cambridge; Professor Martin Buxton, Director of Health Economics Research Group Brunel University; Dr Karl Claxton, Lecturer in Economics, University of York; Professor Sarah Cowley, Professor of Community Practice Development Kings College, London; Mr Chris Evennett, Chief Executive Mid-Hampshire Primary Care Group; Professor Terry Feest, Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit and Chairman of the UK Renal Registry; Professor Gary Ford, Professor of Pharmacology of Old Age / Consultant Physician, Wolfson Unit of Clinical Pharmacology University of Newcastle; Mrs Sue Gallagher, Chief Executive, Merton, Sutton and Wandsworth Health Authority; Dr Trevor Gibbs, Head, Global Clinical Safety & Pharmacovigilance GlaxoSmithKline; Mr John Goulston, Director of Finance, Barts & the London NHS Trust; Professor Philip Home, Professor of Diabetes Medicine, University of Newcastle; Dr Terry John, General Practitioner, The Firs, London; Dr Diane Ketley, Research into Practice Programme Leader NHS Modernisation Agency; Dr Mayur Lakhani, General Practitioner, Highgate Surgery, Leicester and Lecturer, University of Leicester Mr M Mughal, Consultant Surgeon, Chorley and South Ribble NHS Trust; Mr James Partridge, Chief Executive, Changing Faces; Professor Philip Routledge, Professor of Clinical Pharmacology, University of Wales; Professor Andrew Stevens (*Vice Chairman*) Professor of Public Health, University of Birmingham; Dr Cathryn Thomas, General Practitioner, Senior Lecturer Department of Primary Care and General Practice University of Birmingham

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Guidance on the use of taxanes for ovarian cancer. London (UK): National Institute of Clinical Excellence (NICE); 2000 May. (Technology appraisal 3).

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance on the use of paclitaxel in the treatment of ovarian cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Jan. 1 p. (Technology appraisal 55). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- An update of a rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced ovarian cancer. Assessment report. NHS R&D HTA Programme. 2002 Mar 25. 83 p. Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0186. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria are available in Appendix D of the original guideline document.

PATIENT RESOURCES

The following is available:

- Guidance on the use of paclitaxel in the treatment of ovarian cancer. Information for the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Jan. 8 p. (Technology appraisal 55).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0187. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on August 2, 2006.

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